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FATTY TISSUE ATROPHY OF FREE FLAP USED FOR HEAD AND NECK RECONSTRUCTION

MASAKI FUJIOKA, M.D., Ph.D.,* KANA MASUDA, M.D., and YOSHINOBU IMAMURA, M.D.

Background. Many investigators have reported that microsurgical transplanted muscle shows a reduction in volume; however, changes in the size of transplanted fatty tissue have not been studied. The purpose of this study was to describe the degree of fatty tissue atrophy of microsurgical flaps. *Methods.* Nineteen patients who underwent head and neck reconstruction using free flaps between 2003 and 2008 were available for this study. They were divided into an irradiated (8 patients) and nonirradiated (11 patients) group. The free flaps used for reconstruction were rectus abdominal musculocutaneous, anterolateral thigh fasciocutaneous, and forearm flaps. This retrospective study utilized radiographs of magnetic resonance imaging or computed tomography, which were taken two to three and after six months postoperatively. The fatty tissue thickness of free flaps in each magnetic resonance imaging or computed tomography slice was measured. The transplanted fatty tissue thickness of the flap after more than six months was compared with the change in the normal fat thickness of the same slice, to avoid any bias caused by a change in diet due to the general postoperative condition. *Results.* The thickness of transplanted fatty tissue tends to decrease over period of 6–10 months after surgery. In the nonirradiated group, the mean postoperative fatty tissue thickness change in the free flaps was decreased by 15.9% (range, 0.3–31.4%). In the irradiated group, this change in the free flaps was decreased by 20.9% (range, 2.3–39.4%). *Conclusions.* Fatty tissue in free flaps shows atrophy over a period of six to nine months after surgery, and irradiation is more likely to result in severer fatty tissue atrophy. ©2010 Wiley-Liss, Inc. Microsurgery 00:000–000, 2010.

Key words: fatty tissue atrophy; microsurgical free flap; head and neck reconstruction

Microsurgical flaps have become a standard technique for head and neck reconstruction because they provide not only the safe coverage of large tissue defects, but also a cosmetically acceptable appearance.[1–3] It is well-known that transplanted muscle shows a reduction in volume because of the interruption of muscle innervation.[4,5] Flap atrophy is a disadvantage in all types of free flap. On the other hand, fasciocutaneous flaps, which are composed of fascia, fatty tissue, and skin, without muscle, have been believed to allow tissue augmentation with the restoration of symmetry without the problems of atrophy and absorption.[3,6] However, in our experience, even when free flaps do not contain a muscle component, some free fasciocutaneous flaps tend to undergo atrophic changes (see Fig. 1).

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We performed a retrospective study to investigate the degree of fatty tissue atrophy after head and neck reconstruction using free flaps.

PATIENTS AND METHODS

Ninety patients underwent head and neck reconstruction using free flaps between 2003 and 2008 in our medical center. Among these patients, 19 with a mean age of 50 years (range, 26–74 years), could be followed long-term, and their examination data were available for this study. Of these patients, eight received a total dose of 50–62 Gy during radiotherapy for cancer at two to nine weeks postoperatively, and all free flaps were within the radiation field. These eight patients were designed as the irradiated group, and the other 11 were designed as the nonirradiated group. In the irradiated group, causes and locations of defects were mesopharyngeal (three patients), tongue (two patients), oral (one patient), palatal (one patient), and epipharyngeal (one patient) cancers. The free flaps used for reconstruction were rectus abdominal musculocutaneous (RAMC) (four patients), anterolateral thigh fasciocutaneous (ALTFC) (two patients), and forearm (two patients) flaps. In the nonirradiated group, causes and locations of defects were mesopharyngeal (four patients), tongue (two patients), oral (one patient), palatal (one patient), hypopharyngeal (one patient), and epipharyngeal (one patient) cancers, and maxillary neuroblastoma (one patient). The free flaps used for reconstruction were RAMC (seven patients), ALTFC (three patients), and forearm (one patient) flaps. In the surgical procedure, the maximum duration of ischemia (from flap harvest to recirculation after vascular anastomosis) was two hours. No flaps were reinnervated during transfer. All flaps survived successfully without necrosis or infection.

Magnetic resonance imaging (MRI) or computed tomography (CT) of the head was carried out in all patients at 2–3 and 6–10 months postoperatively. The first fat thickness measurement was performed at 2–3 months after surgery to avoid the effect of soft tissue swelling caused by postoperative inflammation. Fatty tissue thicknesses of free flaps in each slice were defined and measured, and we evaluated the degree of atrophy. Measure-

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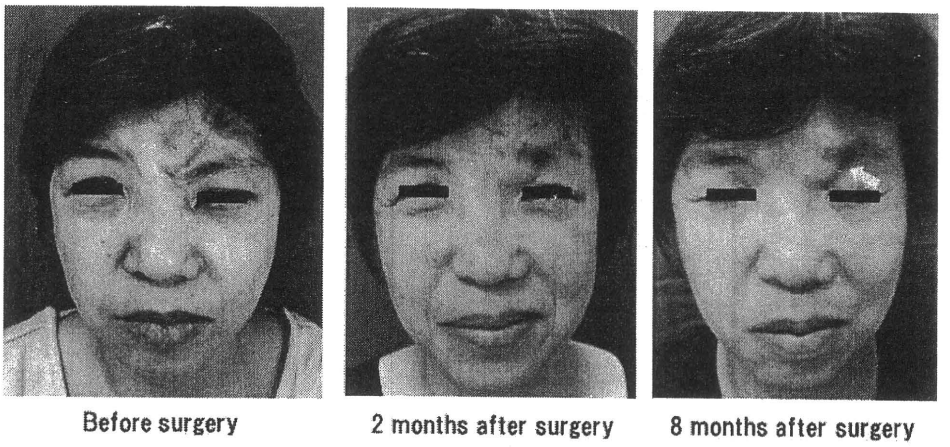

Figure 1. Photographs show the change in fatty tissue thickness of a free anterolateral thigh flap used for reconstruction after neuroblastoma ablation. Left forehead at eight months postoperatively showed depressive deformity due to the patty tissue atrophy (arrow). [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

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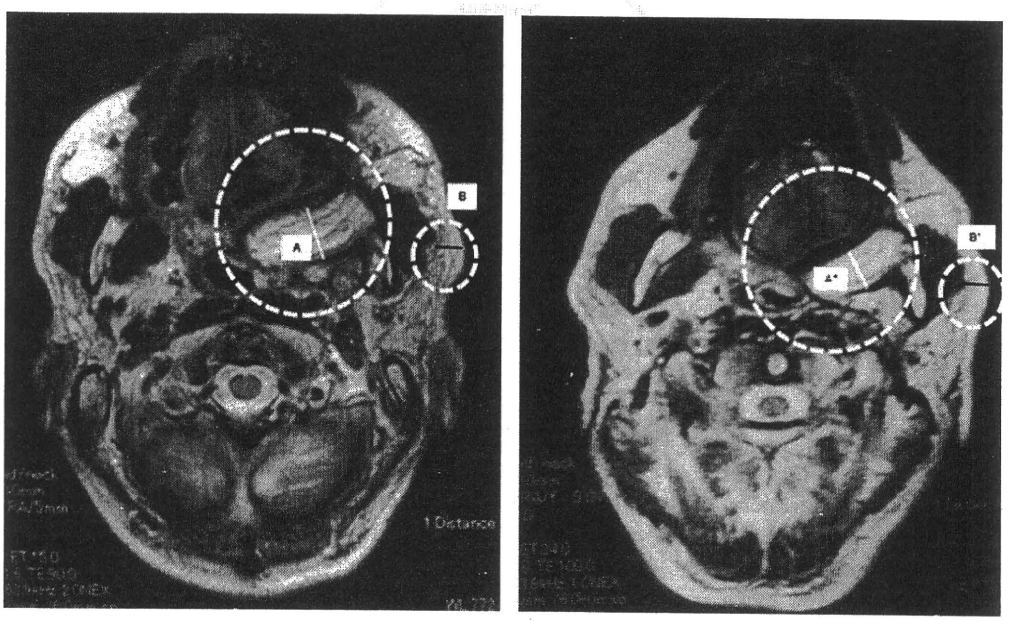

*Figure 2. MRIs show the change in fatty tissue thickness of a free anterolateral thigh fasciocutaneous flap used for reconstruction after mesopharyngeal cancer ablation. The fatty tissue thickness of the free flap in the early phase (**A**) and that in the late phase (**A'**), the normal fat thickness in the early phase (**B**) and that in the late phase (**B'**) were measured.*

ments were performed using a measurement device installed with an image display monitor (Toshiba TFS-01 Image Viewer(DV-R), Toshiba Co. Ltd., Tokyo, Japan). The average values of three measurements taken by the same investigator were adopted. The center of fatty tissue in the flap was decided on as the point of measurement. The change in the normal fat thickness, which could be observed in the same slice of fatty thickness measurement in the free flap, was also measured as a control (see Fig. 2). To avoid an influence (bias) of nutrition due to change in postoperative physical condition, the fatty tissue thickness of the graft at six months or later was corrected based on changes in normal fatty tissue, i.e., Corrected transported fatty tissue thickness measured in the late phase (mm) = transported fatty tissue thickness measured in the late phase (mm) × normal fatty tissue thickness measured in the late phase (mm)/normal fatty tissue thickness measured in the early phase (mm).

Changes in the fatty tissue thickness of the free flap % = (Fatty tissue thickness of the free flap in the late phase with correction in the early phase (mm) − Fatty tissue thickness of the free flap in the early phase (mm))/

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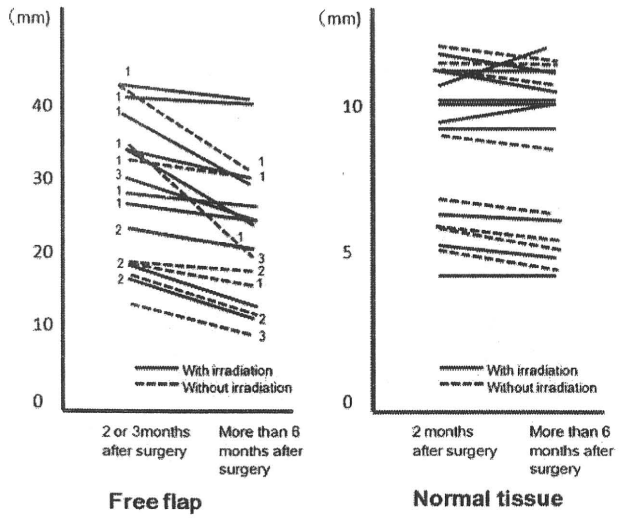

Figure 3. Changes in the fatty tissue thickness of the free flap and normal tissue (with/without irradiation). Numbers in the graph indicate utilized free flaps. Number 1 indicates RAMC flap, 2 indicates ALTFC flap, 3 indicates Forearm flap.

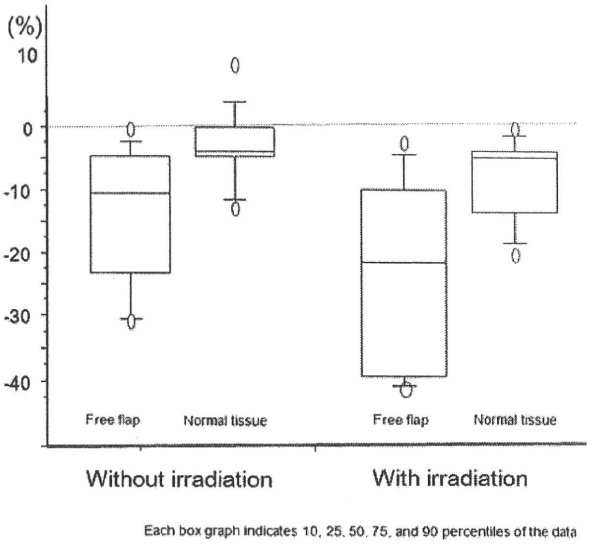

Figure 4. Changes in postoperative fatty tissue reduction of the free flap and normal tissue (with/without irradiation). [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

Fatty tissue thickness of the free flap in the early phase (mm).

Changes in the fatty tissue thickness of the free flap in the early phase and those in the late phase with correction were evaluated in this study. Statistical analysis was performed using the Willcoxon rank sum test to determine the significance of postoperative changes in fatty tissue thickness with/without irradiation. Significance was assumed at $P < 0.05$.

RESULTS

The mean fatty tissue thickness of the transported free flap at 2–3 months was 29.1 mm (range, 11.9–46.3 mm), and that at 6–10 months postoperatively was 24.5 mm (range, 7.2–41.8 mm). The mean postoperative fatty tissue thickness change in all free flaps was by a 19.9% decrease (range, 0.3–39.4% decrease). The mean fatty tissue thickness of the normal skin at 2–3 months was 8.7 mm (range, 4.3–13.0 mm), and that at 6–10 months postoperatively was 8.4 mm (range, 4.2–12.5 mm). The mean postoperative fatty tissue thickness change in normal fat was a 10.0% decrease (range, 0–20.0% decrease). In the nonirradiated group, the mean postoperative fatty tissue thickness change in the free flaps was decreased by 15.9% (range, 0.3–31.4%). In the irradiated group, this change in the free flaps was decreased by 20.9% (range, 2.3–39.4%). The results of both groups showed that fatty tissue in the free flap reduced in volume, and irradiation was more likely to result in fatty tissue atrophy (Figs. 3 and 4). However, there was no significant difference in the thickness reduction between the groups ($P > 0.05$).

DISCUSSION

Microsurgical flap was facilitates the restoration of extensive soft-tissue defects of the head and neck in a one-stage procedure.[3,7] However, these useful free flaps usually undergo long-term volume reduction mainly due to muscle atrophy. Flap atrophy is a disadvantage, as it results in deformity and an asymmetric appearance. Many investigators have studied the degree and mechanism of muscle atrophy in free flaps. Ylä-Kotola et al. evaluated a number of 15 postoperative microsurgical muscle flaps, and concluded that the free flap volume clearly declined.[4] Wolff and Stiller studied the atrophy of free muscle flaps in a rat model, and concluded that signs of muscle atrophy could already be detected in the third postoperative week.[5] However, these findings occurred in the muscle flaps, and studies on fatty tissue atrophy are rare. Free fasciocutaneous flaps, containing no muscle component, have been recommended to avoid facial deformity and asymmetry caused by delayed flap atrophy. Especially, this flap is usually chosen for esthetic facial contour reconstruction because it is believed that fatty tissue in the free flap barely undergoes atrophy, facilitating stable long-term results.[7,8] However, we have noticed that fasciocutaneous flaps may also show atrophy.

Generally, a decrease in the fatty tissue volume results from chronic dieting. Most patients evaluated in this study lost body weight after surgery, probably because of an acute decrease in the dietary intake. Under these conditions, body weight loss occurs mainly due to muscle atrophy, not fat atrophy. Thus, we measured the

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normal fat thickness as a control instead of using the body weight or BMI. We believe that the direct measurement of the normal fat thickness would be a more appropriate control to avoid any bias caused by a change in diet.

Our study revealed that postoperative nonirradiated fatty tissue in free flaps showed a reduction in thickness of about 16%, although efficient circulation was supplied to the flaps after surgery. It is well-known that the combination of endarteritis and chronic ischemia caused by radiation lead to tissue atrophy.[9,10] Thus, the degree of atrophy of irradiated fatty tissue in the free flap is more severe (about 21%) than that of nonirradiated tissue.

Regrettably, we did not clarify the mechanisms of fatty tissue atrophy, which probably involves innervations for the flap, direct tissue damage during surgery, or the 2-hour ischemia.

CONCLUSION

Our study revealed that postoperative fatty tissue in the transferred free flaps reduced in thickness by about 16% in the nonirradiated group and about 21% in the irradiated group, over a period of 6–10 months after surgery, although our findings are limited by the small series of patients and lack of a longer-term follow-up beyond 10 months. Microsurgeons must be aware of postoperative flap atrophy in order to achieve a satisfactory appearance on employing head and neck microsurgical reconstruction or augmentation.

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Linear-Type Orbital Floor Fracture With or Without Muscle Involvement

Hiroki Yano, MD, Yuichi Suzuki, MD, Hiroshi Yoshimoto, MD, Ritsuko Mimasu, MD, and Akiyoshi Hirano, MD

Abstract: The indications for surgical repair of the orbital blowout fracture are controversial. One reason may be case variation among fracture types. We therefore focused on linear-type blowout fractures in this study. The study included 22 consecutive patients with linear-type floor fractures. Demographics, clinical and computed tomographic (CT) findings, surgical timing, postoperative course, and outcome were evaluated. Surgery was performed in 14 patients with diplopia but not enophthalmos. Five patients with severe vertical diplopia were defined as "missing rectus" by CT findings. Residual diplopia remained in 2 patients with "missing rectus," whereas the other 20 patients completely recovered eye motility. In the 9 patients without muscle entrapment, diplopia disappeared within 4 weeks after operation. However, recovery in patients with "missing rectus" took more than 1 month. Thus, the CT finding with or without muscle involvement was crucial for the linear-type blowout fractures. A comprehensive and timely decision based on clinical and radiologic findings is indispensable for satisfactory management as well as postoperative rehabilitation.

Key Words: Blowout fracture, linear fracture, missing rectus, postoperative rehabilitation, Bell phenomenon

(*J Craniofac Surg* 2010;21: 1072–1078)

Management of orbital blowout fracture was relatively conservative,[1,2] it but has recently shifted to favor early surgical repair.[3–5] In this decade, it has been widely accepted that surgical intervention should be performed early in patients with "white-eyed" blowout fractures, severe oculocardiac reflex, and entrapped orbital contents.[6] Surgical procedures at a later stage cannot prevent ischemic damage, and the formation of excess scar tissue causes postoperative complication.[3] More recently, there has been a return to the conservative view of surgery,[7,8] rendering its indication and timing unclear. These fluctuations in management may result from the pathologic complexity of the blowout fracture. Surgical repair for this injury aims to reinstate the orbit with enophthalmos and to restore diplopia. Enophthalmos may result from expansion of the orbit and/or atrophy of the orbital content.[9] Diplopia may result from deformity of the orbit (causing positional changes of the muscles),[10,11] adhesive impingement of the content (disturbing ocular excursion),[2,11] and impairment of the contracting muscle (resulting from neurogenic or myogenic palsy).[11] Because living organisms have the adaptability to compensate for functional defects, the problems noted above, especially diplopia, may be ameliorated with time.

Because the pathologic finding of blowout fractures varies among cases, management cannot be determined solely by the timing of surgery. The indication for surgery must also be defined according to clinical findings and fracture types.[12] Therefore, the aim of this study was to bring the management concept into sharper focus for linear-type blowout fractures, especially with regard to postoperative course. We attempt to elucidate pathologic natures of this type of fracture and propose a postoperative remedy.

PATIENTS AND METHODS

The medical records of 103 consecutive patients of pure-type blowout fractures presented in our department from 2002 to 2007 were examined. Fractures of 22 patients were classified as linear-type fractures of the orbital floor by computed tomographic (CT) findings. Demographics, clinical and CT findings, surgical timing, purpose and procedure, postoperative course, and outcome were explored. In this study, "missing rectus" denoted patients for which coronal CT findings revealed minimal or no inferior rectus muscle density that could be confirmed above the floor.[13,14] For linear fractures, "missing rectus" indicates that the muscle is firmly and tightly entrapped in the fracture site and herniated to the sinus.

Surgical Procedure

Surgery was electively applied depending on the clinical and CT findings.[12] The periosteum was sharply incised and retracted from the rim through an extended subciliary incision. After a linear fracture with entrapment of orbital contents was identified, the herniated tissue was carefully retrieved by cutting out the floor with a fine osteotome. So as not to further damage the tissue, we did not withdraw it from the slit but rather scooped the herniated tissue out from the hole. The orbit was then reconstructed by bone graft. Before skin closure, the release of impingement was confirmed by comparing preoperative and postoperative forced duction tests to avoid iatrogenic gaze restriction. Finally, the incised periosteum was sutured, the skin was closed, and a drain was set in place.

Postoperative Rehabilitation

At 2 or 3 days after the operation, as swelling and pain gradually disappeared, patients could usually obtain a focused field in binocular vision, although this field might be narrow in the beginning. Aftercare was then initiated to expand the focused field: for

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example, chasing a slowly moving finger to the periphery of the field and gazing at a distant point while bending and stretching the neck. However, in severe or juvenile patients, it was sufficiently difficult to exercise binocular vision at the start, so a monoculus was applied to the unaffected eye. This method allowed patients to elicit motion of the affected eye in the early stages while we paid close attention to the possible cause of amblyopia.

Data Analysis

Ocular motility was graded on 5 scales.[12] The correlation coefficient for upgaze and downgaze preoperative motility was obtained using simple regression analysis. Differences in preoperative motility, with or without missing rectus in CT findings, were analyzed in each upgaze and downgaze with the use of the Mann-Whitney *U* test. Simple comparisons of time to surgery, with or without missing rectus, were performed using Student *t* test. Statistical analysis was applied using Microsoft Excel 2003 (http://office.microsoft.com), with Statcel2 add-in software (http://www.oms-publ.co.jp/exl01/howto01.html).

RESULTS

For the 22 linear-type blowout fractures, the mean age of patients was 14.3 years, ranging from 6 to 45 years. Eighteen patients were males and 4 were females. Fractures were due to sports injuries in 9 patients, followed by falling in 6, assault in 4, and traffic accidents in 3. Mean time from injury to presentation was 4.05 days, ranging from 0 to 20 days. Four patients presented numbness of the infraorbital nerve area. In 4 patients, except for CT findings, any clinical findings for further treatment were not observed at our presentation. The other 4 patients showed mild upgaze restriction that spontaneously disappeared during the next few days while patients were under observation. No enophthalmos was observed in the linear fractures.

Fourteen patients underwent surgical intervention to treat diplopia (Table 1). The extent of preoperative vertical restriction varied among patients (Fig. 1). In contrast to textbooks, upgaze restriction was not clearly dominant as compared with downgaze among our patients ($y = 1.01x + 0.30$). Ocular motility was seriously affected in 5 patients with "missing rectus" as revealed by CT findings. Upgaze and downgaze restrictions were more severe in patients with missing rectus compared with those without. The mean time from injury to surgery was 9.7 days, ranging from 0 to 24 days.

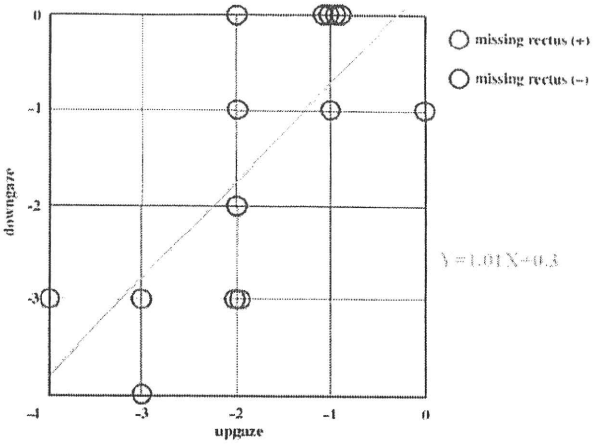

FIGURE 1. Scatter diagram of preoperative ocular motility on upgaze and downgaze in 14 patients who underwent surgery. The simple regression line is indicated in green ($r = 0.730$, $P < 0.003$). Red circles denote patients with "missing rectus," and blue circles denote patients without "missing rectus" in CT findings. (With missing rectus versus without missing rectus: upgaze $P = 0.0093$ and downgaze $P = 0.0027$ by Mann-Whitney *U* test.)

TABLE 1. Clinical Summary of 14 Patients Who Underwent Surgery

Patient No.	Age, y	Sex	Cause	CT Findings		Time to Presentation, d	Complaint	
				Fracture	MR		Enophthalmos	Diplopia
1	10.9	M	Sports	Linear	+	1	−	+
2	8.4	M	Assault	Linear	−	3	−	+
3	24.3	M	Sports	Linear	−	0	−	+
4	9.1	F	Falling	Linear	−	2	−	+
5	11.2	M	Falling	Linear	−	10	−	+
6	17.0	M	Sports	Linear	−	7	−	+
7	16.4	M	Assault	Linear	+	2	−	+
8	18.8	M	Sports	Linear	−	1	−	+
9	9.8	M	Sports	Linear	−	1	−	+
10‡	6.9	F	Sports	Linear	+	20	−	+
11	10.9	M	Sports	Linear	−	4	−	+
12	8.7	M	Falling	Linear	+	0	−	+
13	7.6	M	Falling	Linear	−	7	−	+
14	9.8	M	Falling	Linear	+	2	−	+

*Motility: 0, normal motility; −1, mild restriction; −2, moderate; −3, severe; −4, no motility.
†One or more surgeries were done to release adhesion after the first operation, but diplopia persisted as a sequela.
‡Data for patient 10 were based on the first operation at the previous hospital.
BG indicates bone graft; F, female; M, male; MR, missing rectus; OR, open reduction of the content; V2, infraorbital nerve.

TABLE 2. Time to Surgery From Injury With or Without Missing Rectus

	Time to Surgery, d				
	Mean*	Min	Max	SD	Median
Missing rectus (+)	7.8	0	24	9.45	5
Missing rectus (−)	10.8	5	16	3.11	11

*P = 0.397 by Student t test.

There was no difference between patients with or without missing rectus with regard to time to surgery (Table 2). However, in this series, because some patients were referred to us several days after the injury, the timing of surgery varied. No patient worsened after surgery. Residual diplopia remained only in 2 patients with "missing rectus." These patients underwent surgery at 8 and 24 days. Each of the 20 other patients exhibited completely improved eye movement. The time from surgery to recovery is summarized in Figure 2. Of 14 patients who underwent surgery, 10 fully recovered within 1 month. Patients without missing rectus also completely recuperated within 4 weeks. Conversely, in the patients with missing rectus, recovery took 4 weeks or more: gaze restriction remained in 2 patients. One patient with residual diplopia is described in the next paragraph. Another showed degeneration in and around the inferior rectus muscle on magnetic resonance images 6 months after surgery (Fig. 3). Perimuscular tissue dissection was performed, but the results did not satisfy the patient.

Surgery was performed in 3 of 4 patients who presented with numbness of the infraorbital nerve. One patient experienced numbness after surgery: the numbness was temporal and disappeared without further intervention.

Patient 10: With Missing Rectus and Sequelae

A 6-year-old girl experienced a bruise on her right eye and was previously referred to a surgeon for diplopia 20 days after injury

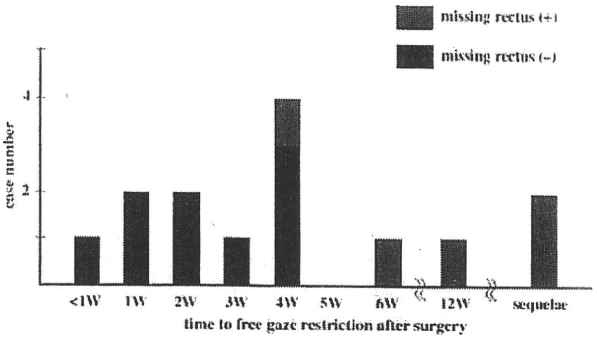

FIGURE 2. Time of surgery to recovery. Red bar indicates patients with "missing rectus," and blue indicates patients without "missing rectus" in CT findings. In patients without "missing rectus," diplopia dissolved within 1 month, but in patients with "missing rectus," diplopia was protracted more than 4 weeks.

(Fig. 4). Surgical correction and bone grafting were performed 24 days after injury, but the vertical restriction of eye movement persisted. The surgeon then referred her to us for further treatment of diplopia 3 months after surgery. We performed surgery to release the adhesion around the inferior rectus muscle, reconstructed again the floor with a large bone graft, and applied traction to the muscle for a week. Ductions improved, but diplopia continued; however, diplopia was not serious enough to warrant strabismus surgery. The CT scans obtained just after injury were checked carefully at a later date and showed missing rectus with a minimally dislocated linear floor fracture.

Patient 14: With Missing Rectus, Without Sequelae

A 9-year-old boy was injured in the right eye after falling from a tree (Fig. 5). The patient visited a local ophthalmologic clinic

Motility*					Numbness	
Up	Down	Time to Surgery, d	Surgery	Time to Recovery	Before Surgery	After Surgery
−3	−4	8	OR + BG	Sequela†	–	–
−1	0	12	OR + BG	4 w	–	–
0	−1	10	OR + BG	1 w	V2	V2
−2	0	10	OR + BG	2 w	–	–
−1	0	16	OR + BG	1 w	–	–
−2	−1	12	OR + BG	4 w	V2	–
−2	−3	5	OR + BG	4 w	V2	V2
−1	−1	8	OR + BG	2 w	–	V2
−1	0	5	OR	3 d	–	–
−2	−3	24	OR + BG	Sequela†	–	–
−2	−2	11	OR + BG	4 w	–	–
−3	−3	0	OR + BG	6 w	–	–
−1	0	13	OR + BG	4 w	–	–
−4	−3	2	OR + BG	12 w	–	–

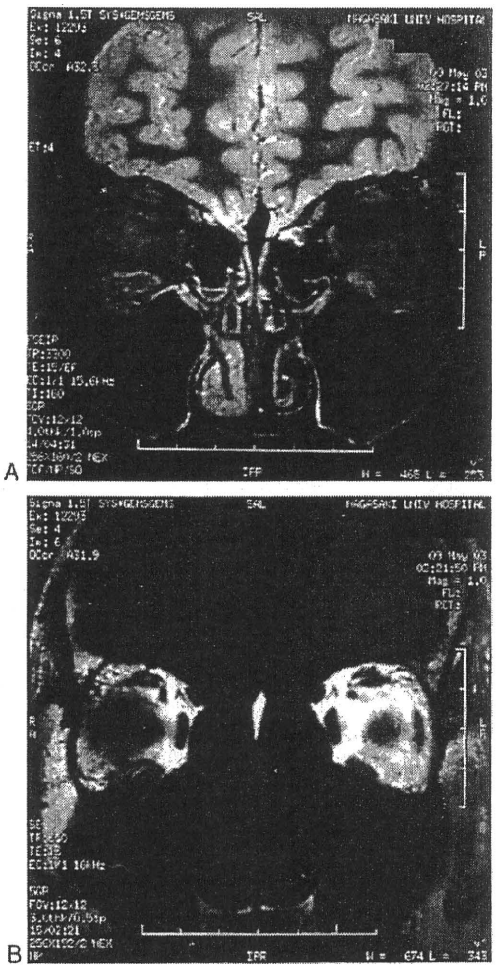

FIGURE 3. Magnetic resonance images 6 months after surgery (short tau inversion recovery [STIR, A] and T1-weighted image [B]). Surgery was performed 8 days after injury, but restriction of the eye movement continued. Herniation was reduced, but fibrous degeneration was seen in and around the inferior rectus muscle. After that, dissection was performed to release the fibrosis, but diplopia persisted.

because of severe diplopia without nausea or vomiting. The ophthalmologist referred him to us with suspicion of a blowout fracture. The referral was not urgent, and the patient visited us as a typical outpatient 2 days after the injury. The vertical restriction of the right eye movement was severe, and CT revealed a muscle incarceration within a linear fracture. Emergency surgery was performed to rescue the missing rectus on the same day. Although the forced duction test after bone grafting revealed good excursion, motility of the right eye was initially discouraging. We advised the patient to wear a monoculus on the left eye for 1 hour, 3 times a day. Motility was slowly but definitely recovered; recovery was completed at 12 weeks after surgery.

DISCUSSION

Blowout fractures lead to 2 disorders: enophthalmos, which affects aesthetics, and diplopia, which impedes function. In general, enophthalmos progressively worsens and diplopia gradually improves over time. The pathologic finding of these 2 disorders is complicated, and living organisms have the adaptability to compensate for functional defects. We therefore focused on the linear-type blowout fracture.

In this study, surgeries were performed in 14 of 18 patients with diplopia at presentation, and almost all were performed for the remaining diplopia within 2 weeks. Surgeries were performed within 2 weeks because, with this type of fracture, diplopia improved little through several days of observation. As many publications about trapdoor fractures have mentioned,[3,16,17] the lack of a spontaneous cure can attribute to mechanical interferences, such as entrapment. Entrapment in linear-type blowout fractures may result in changes that are more focally vulnerable than in other types of fractures. Taken together, these results indicate that the primary pathologic finding of linear-type blowout fracture is dyskinesia resulting from

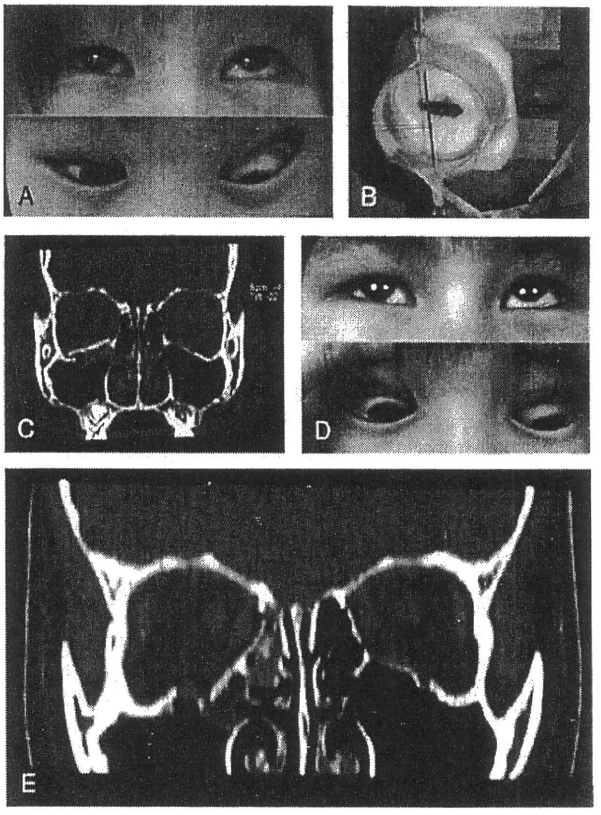

FIGURE 4. Patient with missing rectus and persistent diplopia. Surgical intervention was performed 20 days after injury, but the vertical restriction of eye movement persisted. The patient was referred to us for further treatment after 3 months. A, Eye movement before our operation. Motility was −1 in upgaze and −2 in downgaze. B, Just after our operation. After perimuscular dissection, we applied traction to the inferior rectus muscle for 1 week. C, Coronal CT scan after operation. The floor was reconstructed with a large bone. D, Eight months after our surgery. Motility improved (upgaze, −1; downgaze, −1), but diplopia continued. E, The CT scans just after injury. The right inferior rectus muscle disappeared above the floor.

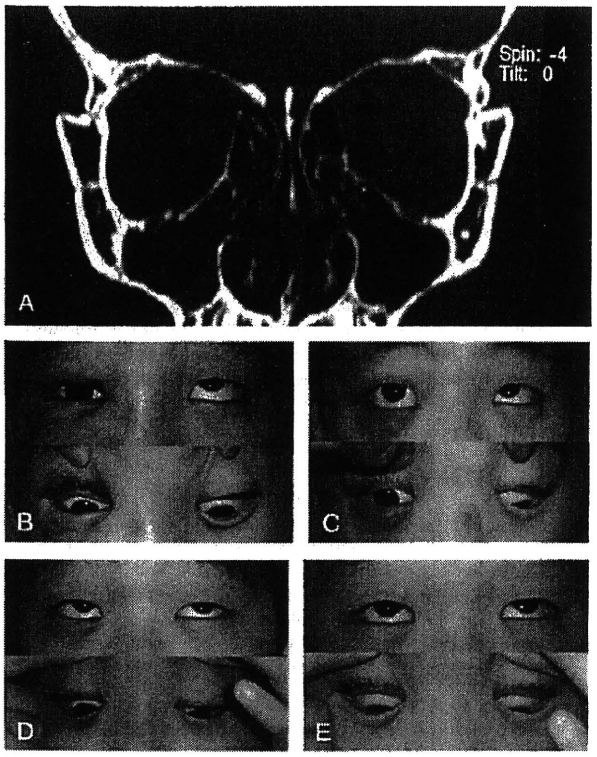

FIGURE 5. Patient with missing rectus but without sequelae. a, Coronal CT scan before surgery. The right inferior rectus muscle partially disappeared above the floor. b, Preoperative gaze restriction (upgaze, −4; downgaze, −3). Two days after injury, the patient presented with a blowout fracture and underwent an emergency operation. The patient did not experience nausea or vomiting from the time of injury until our inspection. c, Two weeks after the operation. Supraduction was well recovered, but infraduction was poor. A monoculus was worn on the left eye for 1 hour, 3 times a day, to exercise the affected right eye (upgaze, −1; downgaze, −3). d, Eight weeks after the operation (upgaze, 0; downgaze, −1). e, It took 12 weeks until the vertical restriction subsided.

adhesive impingement of the content or impairment of the contracting muscle.[11]

Among the patients included in this study, those with 8 or 24 days between the injury and surgery displayed residual diplopia. Other patients with 0, 2, and 5 days between injury and surgery displayed full recovery. Although the critical threshold seems to fall between 5 and 8 days, the degree of injury, as well as the time to surgery, is an important factor that determines the severity of residual diplopia. Computed tomographic images of patient 12 did not reveal a fracture but did indicate a missing rectus[18]: thus, muscle damage was estimated to be greater than that in patient 14. Interestingly, although diplopia in patient 12 disappeared through a 6-week rehabilitation, diplopia in patient 14 did not disappear after 12 weeks. However, even in patient 12, diplopia took more than 4 weeks to heal. These results imply that the damage already presents at injury,[11] and early surgery prevents spreading it (ie, scar adhesion) around the fracture. As in myocardial infarction, if damage is minimal and appropriate management is undertaken in a timely fashion, the remaining healthy muscle compensates for damage-related defects. In blowout fractures, fortunately, muscle entrapment in the linear fracture is rare.[12,19] If muscle entrapment is observed, it involves only limited portions of the muscle, leaving more than half of the muscle belly still intact.[18] Some advocate early surgery to prevent ischemic alterations of an impinged muscle.[13,16] However, because muscle ischemia becomes irreversible within hours, it may be nearly impossible to perform the operation after definitive diagnosis.[3,19] We believe that blood flow may not be completely absent in muscles entrapped in blowout fractures. Regions of ischemic necrosis and unstable regions such as the zone of stasis in thermal trauma[20] may coexist around the fracture site. Therefore, because missing rectus recovery is time-consuming, early surgery and early rehabilitation are indispensable for such fractures. However, persistent gaze restriction might be unavoidable for patients with severe muscle damages beyond a critical point even with an urgent surgery. Although surgery for missing rectus is time-intensive, the procedure for linear fractures must be simpler than in other types because dissection around the infraorbital nerve is rarely required and the orbital buttress remains intact in most linear-type fractures.[12]

During the postoperative course of some blowout fractures, a paradoxical eye movement was observed (Fig. 6). This odd phenomenon was observed during the early postoperative phase. After dissolving the impingement in the fracture by surgical intervention, it may result from compensation or disturbance of the afferent nervous signaling by stretch receptors[21,22] in the orbit. In patients with missing rectus, early effective rehabilitation is important for fully recovered ductions because infraduction restriction initially remains serious despite the removal of mechanical interference. When binocular vision exercises are difficult for severely injured or juvenile patients, a monoculus on the unaffected eye during the early phase of postoperative recovery may help to rehabilitate the affected eye motion while avoiding amblyopia in children.

In any type of blowout fracture including medial wall fractures, vertical gaze, especially upgaze, impairments are more common than lateral gaze restriction. Linear-type or closed trapdoor fractures may be frequent in the floor because of the structural differences in the paranasal sinuses (ethmoid cells vs maxillary sinus). This specificity may also be related to the Bell phenomenon at injury

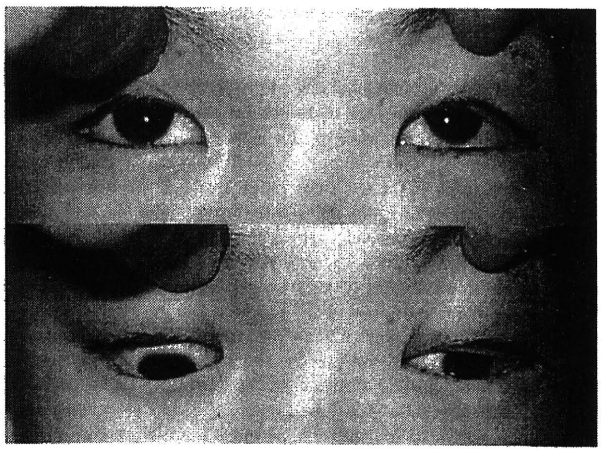

FIGURE 6. Paradoxical eye movement after the blowout surgery (patient 12; 3 days after surgery). Supraduction of the affected eye was superior to that of the intact eye in the early phase after surgery. This overactivity of the affected side was also occasionally observed in the late phase after surgery.

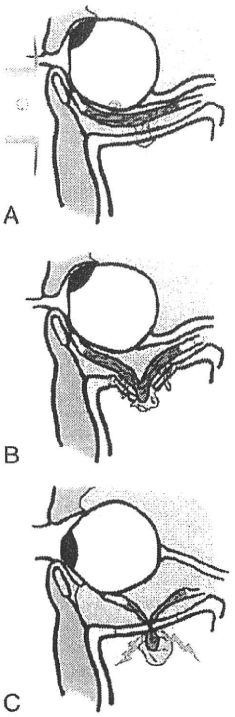

FIGURE 7. Role of Bell phenomenon in the linear-type blowout fracture. A, Almost all patients closed their eyes firmly at injury, and the supraduction caused by Bell phenomenon results in lengthening of the inferior rectus. The muscle is brought to the front of the eye and to frequent sites of fractures. B and C, After breaking the floor, the muscle is herniated through the fracture site. Then the door is closed by the force of its elasticity. More damage may occur on closing the trapdoor by the returning force that may assist closing the door when the eye returns to the normal position. (For a better understanding, the fracture line is depicted in the coronary direction. Clinically, most linear-type fractures in the floor occur in the sagittal direction.)

(Fig. 7).[12] Almost all patients with blowout fractures have experienced blunt injuries and are therefore forced to close their eyes firmly just before injury. Closing the eyes results in supraduction (Bell phenomenon), which lengthens the inferior rectus and brings the muscle in front of the eye's equatorial plane. If fracture occurs under the muscle leading to herniation through the fracture site, more damage may occur on closing the trapdoor when the eye returns to the primary position. The returning force may assist in closing the door, which may become lodged and damage itself at the fracture edge. In addition, Iliff et al[11] reported that the inferior rectus muscle near the apex was delicate in comparison to the denser connective tissue around the muscle at its global insertion. Some reports have noted muscle swelling on the floor without the identification of missing rectus in CT findings.[11,23,24] The rectus may be damaged on return to the primary position, similar to degloving injury. This can occur in any fractures with sharp edges. However, because punched out or burst-type fractures may result in orbital decompression in a sense, early reconstruction of the floor in such cases may worsen the swollen muscles by a surgical invasion in addition to posttraumatic stress.[12]

In conclusion, in patients without "missing rectus," surgery for diplopia in linear-type blowout fractures can be postponed for several days until swelling has decreased. This is because orbital surgeries are technically easier after the swelling has subsided and planned surgeries are preferable with regard to economics considerations.[12] In patients with "missing rectus," surgery should be performed immediately to save unstable regions of the orbital muscle because recovery time and sequelae were correlated to both degree of the damage and time to surgery. A comprehensive and timely decision based on clinical and radiologic findings is required for a satisfactory management. If surgeons waver in their decision regarding borderline findings, such as in patients with severe vertical restriction but unclear missing rectus on CT images, currently, surgery should be performed immediately for linear-type fractures. Compared with other types of fractures, the linear-type blowout fracture less frequently exhibits spontaneous healing. Surgery will be needed, whether the patients are observed for several days, in this type of fractures.

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CASE REPORT

Isoniazid-triggered pure red cell aplasia in systemic lupus erythematosus complicated with myasthenia gravis

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Abstract A 47-year-old woman who had been treated for systemic lupus erythematosus (SLE) with myasthenia gravis (MG) was admitted to our hospital with acute onset of severe anemia after administration of isoniazid. Pure red cell aplasia (PRCA) was confirmed by elevated serum iron levels, reticulocytopenia and bone marrow aspiration showing a remarkable reduction of erythroblasts. Finally, cyclosporine A successfully improved PRCA. Although both SLE and MG have the potential complication of PRCA, we report here a case of isoniazid-triggered PRCA.

Keywords Pure red cell aplasia · Isoniazid · Systemic lupus erythematosus · Myasthenia gravis · Cyclosporine A

Abbreviations

CyA	Cyclosporine A
SLE	Systemic lupus erythematosus
MG	Myasthenia gravis
PRCA	Pure red cell aplasia

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Introduction

Pure red cell aplasia (PRCA) is an uncommon hematological disorder [1]. Severe anemia in PRCA is associated with a marked reduction of reticulocytes and an absence of erythroblast in bone marrow [1]. Although primary PRCA is a chronic hematological disorder, secondary PRCA can be caused by viral infections, autoimmune disorders or drugs [2]. Autoimmune disorders such as systemic lupus erythematosus (SLE) and myasthenia gravis (MG) complicated with thymoma are occasionally reported to be predisposed to PRCA [3]. A possible cause is drug-induced PRCA which is reported in up to 5% of cases. Here, we report a rare case of isoniazid-triggered PRCA in a patient with SLE and MG.

Case report

A 47-year-old woman had been diagnosed with SLE and was treated with 20 mg of oral prednisolone in 1995. Although she was taking 2 mg of oral prednisolone daily, she developed ocular type MG with right blepharoptosis that showed a positive tensilon test and positive acetylcholine receptor binding antibodies, without thymoma. Because she experienced diplopia, she began taking 180 mg of pyridostigmine bromide, 10 mg of oral prednisolone and 200 mg of mizoribine in 2001. As of 2006, she was taking 3 mg of tacrolimus and 11 mg of oral prednisolone daily. Because her mother died of pulmonary tuberculosis, she began taking prophylactic isoniazid on 26th September 2008. On 4th October she became extremely fatigued and had heart palpitations while walking the dog. Upon admission to the hospital, she became fatigued with a low-grade fever and was breathless with exertion.

Her hemoglobin level was significantly reduced from 10.8 g/dl on 3rd September to 5.8 g/dl on 24th October (Fig. 1) with remarkable reduction of reticulocytes (1,000/μl; normal, 25,000–75,000/μl), normal leukocyte and platelet counts. An increase in serum iron (225 μg/dl; normal, 48–154 μg/dl) with a decrease in unsaturated iron binding (13 μg/dl; normal, 108–325 μg/dl) was found along with normal haptoglobin levels (70.3 mg/dl). Serum folic acid and vitamin B12 levels were within normal limits. IgM and IgG antibodies specific for parvovirus B19 and hepatitis B antigen were negative. Furthermore, both parvovirus B19 and Epstein–Barr virus deoxyribonucleic acid was not detected by polymerase chain reaction. Serum IgG and anti-double stranded deoxyribonucleic acid antibodies were elevated to 2,030 mg/dl (normal, 870–1,700 mg/dl) and 88.4 U/ml (normal <12 U/ml) with reduced complement 3 (59.8 mg/dl; normal, 65–135 mg/dl) and normal C-reactive protein (0.04 mg/dl; normal, <0.17 mg/dl). Chest computed tomography in September 2008 showed neither thymoma nor swelling of the lymph nodes.

Because acute progression of anemia was observed immediately after taking isoniazid, its administration was ceased on 24th October. To conduct the hematological differential diagnosis, bone marrow aspiration was performed on 29th October, resulting in the diagnosis of PRCA according to Casadevall criteria [4] accompanied by a decrease in erythroblast. In addition, no malignant cells were observed with normal myeloid cells and megakaryocytes. Although nine cycles of red blood cell transfusion were performed, administration of daily cyclosporine A (CyA) was required due to the protracted recovery of PRCA. When a trough level of 157.3 ng/ml was reached using 300 mg of CyA, the hemoglobin and reticulocyte counts were gradually improved without blood transfusion (Fig. 1). On 20th February 2009, reticulocyte counts reached 147,000 with a concomitant improvement of serum iron levels to 130 μg/dl and hemoglobin levels to 8.3 g/dl.

Discussion

Liver dysfunction and peripheral neuropathy are known to be common adverse side effects of isoniazid; however, isoniazid-induced PRCA has been rarely reported. Some reports [5, 6] showed isoniazid-induced PRCA which was rapidly improved by withdrawal of the drug. Erslev et al. [7] previously reviewed the pathologic condition of PRCA, in which they listed 26 drugs as causative agents

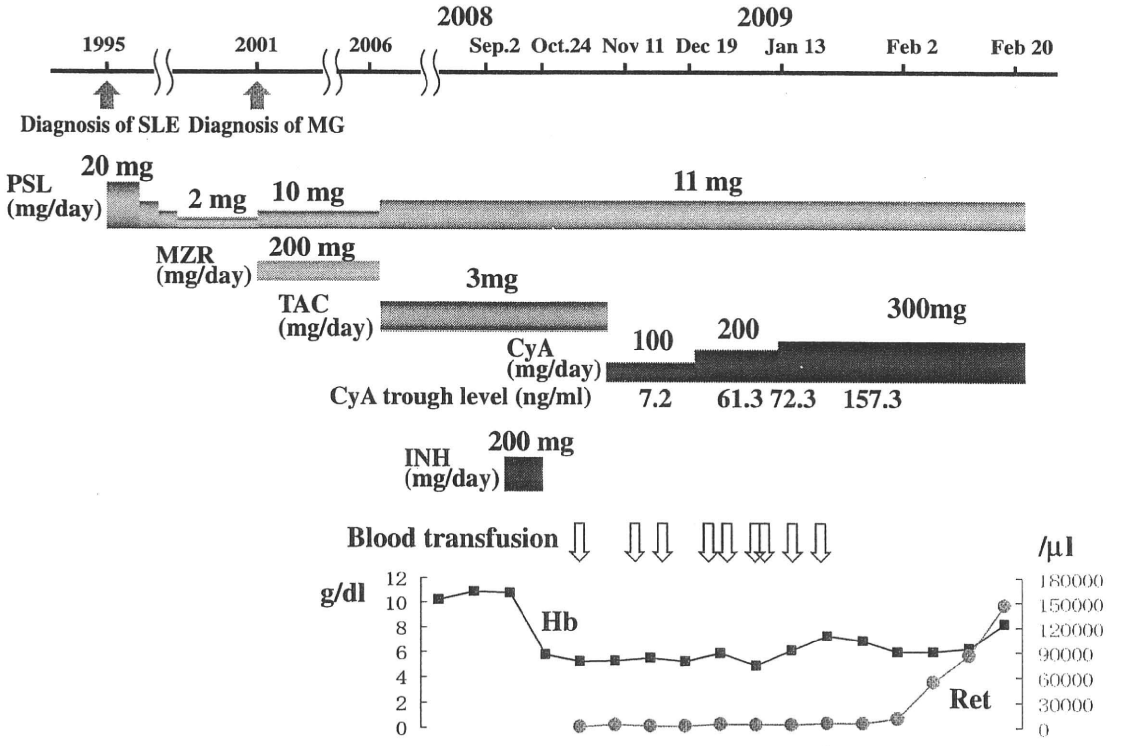

Fig. 1 Clinical course of pure red cell aplasia (PRCA) of the patient with systemic lupus erythematosus (SLE) combined with myasthenia gravis (MG). The patient was pretreated with 11 mg of oral prednisolone and 3 mg of tacrolimus for SLE and MG. Immediately thereafter she took 200 mg of isoniazid and severe anemia appeared with remarkable reduction of reticulocytes, which was confirmed as PRCA by bone marrow aspiration. Since discontinuation of isoniazid and repeated blood transfusions were not effective for recovery of anemia, cyclosporine A (CyA) was substituted for tacrolimus. After the trough level of CyA reached 157.3 ng/ml, the reticulocyte and hemoglobin levels were recovered without additional blood transfusions. *PSL* prednisolone, *MZR* mizoribine, *TAC* tacrolimus, *INH* isoniazid

including isoniazid for PRCA. Although the detailed mechanism of drug-induced PRCA remains unclear, diphenylhydantoin, an anti-epileptic agent, was shown to be a possible inducer of PRCA through a specific antibody toward the agent [8]. Thus, a similar mechanism of antibody-dependent cytotoxicity might account for isoniazid-related PRCA.

Autoimmune diseases such as SLE or MG can be associated with the pathogenesis of PRCA. Mizobuchi et al. [9] reviewed 28 published cases of PRCA that were complicated with MG and thymoma. Although MG could be complicated with PRCA with or without a thymoma, a T cell-mediated immunological response is assumed in both cases. The association between PRCA and SLE is relatively rare. Habib et al. [10] reported that most of the cases of PRCA were diagnosed after, or concomitantly with, the diagnosis of SLE. However, the characteristics of SLE were reported to be similar despite the diagnosis of PRCA. As to the mechanism of PRCA in SLE, a T cell-mediated immune response is a possibility in both SLE and MG. In support of this idea, Arcasoy et al. [11] conducted hematopoietic progenitor cell assays in which the defect of burst-forming unit-erythroid colony formation was restored by T cell depletion.

Preferential utilization of CyA for treatment of PRCA has been established due to its effectiveness. A nationwide cohort study of CyA treatment for acquired PRCA was done in Japan [12]. The results showed a sustained, relapse-free survival in CyA-containing regimens compared to treatment with corticosteroid alone. CyA has the potential to inhibit T cell activation through inhibition of nuclear translocation of the nuclear factor of activated T cells (NF-AT). Thus, in our case, T cell-mediated cytotoxicity of the underlying autoimmune mechanism might be an appropriate indication.

In summary, the present case of PRCA is thought to be triggered by isoniazid due to its clinical course. Considering the prolonged recovery period after administration of isoniazid, we insist that existence of both MG and SLE protracted the course of PRCA based on a T cell-mediated mechanism in our case. Therefore, isoniazid would be merely an inducer of T cell-mediated cytotoxicity. Additional studies of drug-related PRCA under the presence of autoimmune diseases are required to elucidate the mechanism of action in isoniazid-induced PRCA.

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ORIGINAL ARTICLE

Comparative analysis of remission induction therapy for high-risk MDS and AML progressed from MDS in the MDS200 study of Japan Adult Leukemia Study Group

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Abstract A total of 120 patients with high-risk myelodysplastic syndrome (MDS) and AML progressed from MDS (MDS–AML) were registered in a randomized controlled study of the Japan Adult Leukemia Study Group (JALSG). Untreated adult patients with high-risk MDS and MDS–AML were randomly assigned to receive either idarubicin and cytosine arabinoside (IDR/Ara-C) (Group A) or low-dose cytosine arabinoside and aclarubicin (CA) (Group B). The remission rates were 64.7% for Group A (33 of 51 evaluable cases) and 43.9% for Group B (29 out of 66 evaluable cases). The 2-year overall survival rates and disease-free survival rates were 28.1 and 26.0% for Group A, and 32.1 and 24.8% for Group B, respectively. The duration of CR was 320.6 days for Group A and 378.7 days for Group B. There were 15 patients who lived longer than 1,000 days after diagnosis: 6 and 9 patients in Groups A and B, respectively. However, among patients enrolled in this trial, intensive chemotherapy did not produce better survival than low-dose chemotherapy. In conclusion, it is necessary to introduce the first line therapy excluding the chemotherapy that can prolong survival in patients with high-risk MDS and MDS–AML.

For the Japan Adult Leukemia Study Group.

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1 Introduction

Myelodysplastic syndrome (MDS) is a group of disorders in which abnormalities occur at the level of hematopoietic stem cells [1], leading to disturbance in the production of blood cells characterized by ineffective hematopoiesis [2], decrease in the number of peripheral blood cells and morphological/functional abnormalities in blood cells [3]. Allogeneic hematopoietic cell transplantation (allo-HCT) is the most effective curative therapy for acute myeloid leukemia (AML) and myelodysplastic syndromes (MDS) [4]. However, for patients with high-risk MDS (those with refractory anemia with excess of blasts in transformation (RAEB)-t and some patients with RAEB) and patients with acute myeloid leukemia progressed from MDS (MDS–AML), chemotherapy aimed at remission is being used. The reasons for this are that MDS often affects elderly people [5], suitable donors are not always available at the time of disease onset, the necessity of pretransplant conditioning chemotherapy is controversial [6, 7] with a lack of sufficient evidence, and the optimal timing for transplantation varies widely depending on disease type [8].

On the other hand, reduced-intensity conditioning has extended the use of allo-HSCT to patients otherwise not eligible for this treatment due to older age or frailty [9]. However, allo-HSCT using traditional myeloablative preparative regimens is not easily tolerated by the elderly or frailer patient, and may lead to prohibitive treatment-related mortality rates. Most patients treated in the past were younger and devoid of comorbid clinical conditions. Novel reduced-intensity regimens have recently made allogeneic transplants applicable to the elderly, providing the benefit of the graft-versus-leukemia effect to a larger number of patients in need [10].

Low-dose chemotherapy, which has been used in clinical practice for 20 years, reduces the number of myeloblasts, improves pancytopenia and induces remission not only in MDS patients but also in some MDS–AML patients [11]. Common antineoplastic agents used in low-dose chemotherapy include cytosine arabinoside (Ara-C), aclarubicin (ACR), melphalan and etoposide. Nevertheless, despite improved Ara-C and regimens, the prognosis of AML in patients beyond 60 years of age remains dismal [4]. Low-dose antineoplastic drug therapy is still being used in some patients with MDS, which is common in elderly people, especially when the patient is at risk due to poor general condition or organ disorder [12].

The Japan Adult Leukemia Study Group (JALSG) previously conducted a pilot study for the treatment of high-risk MDS and MDS–AML to compare low-dose monotherapy with low-dose Ara-C plus granulocyte colony-stimulating factor (G-CSF) and multiple drug therapy with Ara-C plus Mitoxantrone plus VP-16. Later, JALSG conducted studies using a single protocol (JALSG MDS96) in 1996, in which remission induction and post-remission therapies using Ara-C and IDR in patients with high-risk MDS (RAEB-t) and in those with MDS–AML were performed, after which the efficacy and safety of these therapies were evaluated [13]. Furthermore, a randomized controlled study (JALSG MDS200) of intensive chemotherapy (IDR/Ara-C) or low-dose chemotherapy (CA) for high-risk MDS was also performed by JALSG.

Here, we present and analyze the results of the JALSG MDS200 study to assess and evaluate the validity of the MDS200 protocol for MDS treatment.

2 Patients and methods

2.1 Patient eligibility

A total of 120 patients were initially registered into the JALSG MDS200 study between June 2000 and March 2005. They were assigned into two groups, namely, Groups A and B (Table 1). Patients aged 15 years or more and diagnosed as having high-risk RAEB with high International Prognostic Scoring System score [14], RAEB-t or MDS-AML were eligible for this study. MDS–AML denotes secondary AML transformed from MDS.

Other eligibility criteria were as follows: patients with a performance status (PS) of 0–2 (ECOG); patients whose key organs other than the bone marrow retain intact function; patients who have not undergone any chemotherapy, except for pretreatment that does not affect the outcome of the main therapy; and patients who have given informed consent. Informed consent was obtained after carefully explaining the protocol and before registration.

2.2 Study protocol

The MDS200 protocol (Fig. 1) was designed based on the results of MDS96, and involved a dose-attenuation plan and allowed a wider range of chemotherapy. Patients were randomly assigned to either Group A or B.

In therapy A, the dose was adjusted according to a dose attenuation plan based on the presence of risk factors. The following 3 factors were regarded as risk factors: (1) Age ($\geq$60 years), (2) hypoplastic bone marrow and (3) PS $\geq$ 2. Patients with no risk factor received the standard dose, those with 1 risk factor received 80% of the dose and those with 2 or more risk factors received 60% of the dose (equivalent to the dose of MDS96). In therapy B, the use of

Table 1 Characteristics of patients

Group	A ($n = 53$)	B ($n = 67$)	P value (A vs. B)
Age (range)	63 (23–77)	61 (32–81)	0.505
Gender			
Male	37	52	0.332
Female	16	15	
Disease type			
HR-RAEB	4	11	0.269
RAEB-T	22	29	
MDS–AML	27	27	
Infection			
Presence	10	11	0.726
None	43	56	
Karyotype[a]			
Good	23 (44.2%) $n = 52$	21 (33.9%) $n = 62$	0.524
Int	11 (21.2%)	15 (24.2%)	
Poor	18 (34.6%)	26 (41.9%)	
PB (range)			
WBC (/μL)	2,500 (700–64,240)	2,720 (600–43,700)	0.665
Hb (g/dL)	8 (4.7–12.6)	7.9 (4.4–12.7) $n = 66$	0.562
Plt (/μL)	5.8 (0.2–31.4)	5.9 (0.5–36.7)	0.363
BM (range)			
Blast (%)	30 (4–95) $n = 51$	24.2 (1.9–96) $n = 66$	0.171
Biochemical data (range)			
LDH (IU/L)	296 (132–882)	303.5 (111–906) $n = 66$	0.998
CRP (mg/dL)	0.5 (0–20.2)	0.35 (0–11.7) $n = 66$	0.292

Patients who met all of the inclusion criteria and did not meet any of the stated exclusion criteria were included the study. The disease types were classified by FAB classification

Statistical analysis between Group A and Group B was done using χ^2 test or Mann–Whitney U-test

MDS myelodysplastic syndrome, *HR-RAEB* high risk-refractory anemia excess of blasts with high International Prognostic Scoring System Score, *RAEB-T* refractory anemia excess of blasts in transformation, *MDS–AML* MDS overt leukemia, *WBC* white blood cell, *Hb* hemoglobin, *Plt* platelet, *LDH* lactate dehydrogenase, *CRP* C-reactive protein, *PB* peripheral blood, *BM* bone marrow

[a] Shows IPSS risk

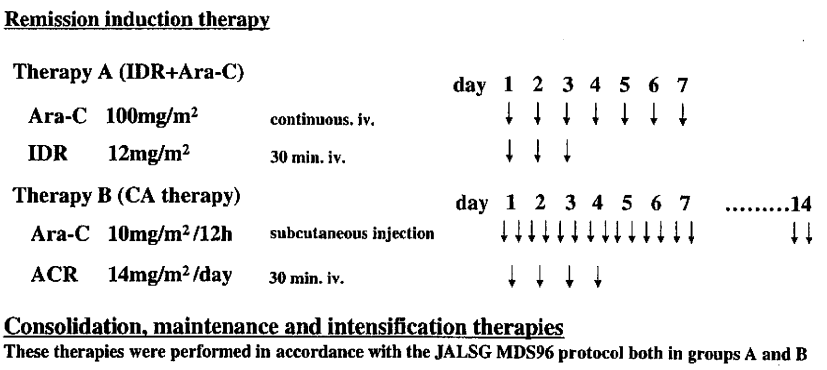

Fig. 1 Japan Adult Leukemia Study Group—myelodysplastic syndrome (JALSG MDS200 Protocol). In therapy A, the dose was adjusted according to a dose attenuation plan based on the presence of risk factors. The following 3 factors were regarded as risk factors: (1) Age (≥60 years), (2) hypoplastic bone marrow and (3) PS ≥ 2. Patients with no risk factor received the standard dose, those with 1 risk factor received 80% of the dose, and those with 2 or more risk factors received 60% of the dose (equivalent to the dose of MDS-96). In therapy B, the use of CAG therapy involving co-administration of G-CSF was allowed. *IDR* idarubicin, *Ara-C* cytosine arabinoside, *ACR* aclarubicin, *G-CSF* granulocyte colony-stimulating factor, *iv* intravenous injection, *min* minutes